



CLINICAL SCIENCE

Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme

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ABSTRACT

Objectives This integrated analysis presents the safety profile of upadacitinib, a Janus kinase inhibitor, at 15 mg and 30 mg once daily in patients with moderately to severely active rheumatoid arthritis (RA).

Methods Treatment-emergent adverse events (TEAEs) and laboratory data from five randomised, placebo- or active-controlled phase III trials of upadacitinib for patients with RA were analysed and summarised. Exposure-adjusted event rates are shown for placebo (three trials; 12/14 weeks), methotrexate (two trials; mean exposure: 36 weeks), adalimumab (one trial; mean exposure: 42 weeks), upadacitinib 15 mg (five trials; mean exposure: 53 weeks) and upadacitinib 30 mg (four trials; mean exposure: 59 weeks).

Results 3834 patients received one or more doses of upadacitinib 15 mg (n=2630) or 30 mg (n=1204), for a total of 4020.1 patient-years of exposure. Upper respiratory tract infection, nasopharyngitis and urinary tract infection were the most commonly reported TEAEs with upadacitinib. Rates of serious infection were similar between upadacitinib 15 mg and adalimumab but higher compared with methotrexate. Rates of herpes zoster and creatine phosphokinase (CPK) elevations were higher in both upadacitinib groups versus methotrexate and adalimumab, and rates of gastrointestinal perforations were higher with upadacitinib 30 mg. Rates of deaths, malignancies, adjudicated major adverse cardiovascular events (MACEs) and venous thromboembolic events (VTEs) were similar across treatment groups.

Conclusion In the phase III clinical programme for RA, patients receiving upadacitinib had an increased risk of herpes zoster and CPK elevation versus adalimumab. Rates of malignancies, MACEs and VTEs were similar among patients receiving upadacitinib, methotrexate or adalimumab.

Trial registration numbers SELECT-EARLY: NCT02706873; SELECT-NEXT: NCT02675426; SELECT-COMPARE: NCT02629159; SELECT-MONOTHERAPY: NCT02706951; SELECT-BEYOND: NCT02706847.

INTRODUCTION

Oral targeted synthetic disease-modifying anti-rheumatic drugs, such as Janus kinase inhibitors (JAKis), have demonstrated at least similar efficacy to biologic disease-modifying antirheumatic drugs (bDMARDs) in randomised controlled trials (RCTs) as treatment for rheumatoid arthritis (RA). Shared

Key messages

What is already known about this subject?

- Upadacitinib is a Janus kinase (JAK) inhibitor which has been studied across a spectrum of patients with moderately to severely active rheumatoid arthritis (RA); the efficacy of upadacitinib has been reported from the five randomised controlled trials (RCTs) which comprise the phase III SELECT clinical programme.
- JAK inhibitors have been associated with several safety risks, including herpes zoster, serious and opportunistic infections, thromboembolic events and changes in laboratory parameters.

What does this study add?

- This integrated safety analysis of upadacitinib, based on more than 3500 patients and 4000 patient-years of exposure, supports an acceptable safety profile for treatment of patients with RA and reports no new safety risks compared with other JAK inhibitors.
- Upadacitinib 15 mg once daily had a similar safety profile to that of adalimumab for rates of serious infections, malignancies, major adverse cardiovascular events and venous thromboembolic events but higher rates of herpes zoster and creatine phosphokinase elevations.

How might this impact on clinical practice or future developments?

- The results of this integrated safety analysis of five RCTs suggest that upadacitinib has a similar safety profile to other JAK inhibitors as demonstrated in their clinical development programmes.

decision-making between physicians and patients regarding treatment selection requires understanding benefits and risks, including the safety profiles of treatment options.

Upadacitinib is a JAKi engineered for increased selectivity for JAK1 over JAK2, JAK3 and tyrosine kinase 2.¹ Upadacitinib 15 mg once daily was recently approved in the USA and Europe for

patients with moderately to severely active RA who are intolerant of or have had an inadequate response to methotrexate (MTX).^{2,3} Efficacy and safety of upadacitinib were studied in patients with moderately to severely active RA in five pivotal phase III RCTs: SELECT-NEXT,⁴ SELECT-BEYOND,⁵ SELECT-MONOTHERAPY,⁶ SELECT-COMPARE⁷ and SELECT-EARLY.⁸ Here, we report an integrated analysis of the safety profile of upadacitinib 15 and 30 mg once daily from these trials.

METHODS

Studies

Data were pooled from the five SELECT trials (online supplemental table S1), which evaluated upadacitinib administered with or without background conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in patients with moderately to severely active RA, including MTX-naïve patients and those with an inadequate response or intolerance to one or more csDMARDs or bDMARDs.

Patients aged ≥ 18 years with active RA (≥ 6 swollen and ≥ 6 tender joints and high-sensitivity C-reactive protein ≥ 3 mg/L (≥ 5 mg/L in SELECT-EARLY⁸ and SELECT-COMPARE⁷ at screening) who met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria were enrolled.⁹ Additional inclusion criteria in SELECT-EARLY and SELECT-COMPARE were erosive joint damage and/or autoantibody seropositivity.^{7,8} Exclusion criteria are listed in the online supplemental material. Patients were tested for tuberculosis (TB) at screening; those with latent TB could enrol after initiating appropriate prophylactic treatment.

Patient and public involvement

Patients and the public were not involved in the design or analysis of this study.

Dosing

Depending on the study, patients received extended-release upadacitinib (15 or 30 mg once daily), placebo, MTX or subcutaneous adalimumab (40 mg every other week), as monotherapy or in combination with background csDMARDs. Patients were not permitted to switch between upadacitinib doses. MTX-naïve patients randomised to MTX started oral medication at 10 mg/week (7.5 mg/week in China and Japan) and were titrated to a maximum of 20 mg/week (15 mg/week in Japan) through week 8, as tolerated.

Safety assessments

Data from patients who received one or more doses of study drug were integrated into five analysis sets (online supplemental table 1). The placebo-controlled analysis set included short-term data from patients who remained on stable doses of their current csDMARDs through week 12 (SELECT-NEXT⁴ and SELECT-BEYOND⁵ or week 14 (SELECT-COMPARE).⁷ The remaining four analysis sets included longer-term data up to 2.5 years. The MTX-controlled analysis set included pooled data from SELECT-EARLY^{8,10} and SELECT-MONOTHERAPY,⁶ censored at rescue. The adalimumab-controlled analysis set included patients randomised or rescued to adalimumab in SELECT-COMPARE.⁷ Upadacitinib 15 mg data were pooled from all five studies; and upadacitinib 30 mg data were pooled from four studies (all except SELECT-COMPARE).

Adverse events (AEs) were assessed based on Outcome Measures in Rheumatology (OMERACT) criteria. Potentially clinically significant laboratory values (grades 2, 3 or 4) were

determined by OMERACT criteria, except for creatine phosphokinase (CPK) and serum creatinine, which were based on the National Cancer Institute's Common Toxicity Criteria v4.03. Potentially clinically significant outliers were based on patient laboratory values meeting the criteria on one or more occasions.

Adverse events of special interest (AESIs) were selected due to their higher prevalence among RA populations, as a customary concern for immunomodulators, or because they were labelled/emerging risks with other JAKis. AEs were identified using the standardised Medical Dictionary for Regulatory Activities (MedDRA) query or company MedDRA query search criteria. A treatment-emergent adverse event (TEAE) was defined as an AE with onset on or after the first dose of study drug and no more than 30 days (70 days for adalimumab) after the last dose of study drug.

An independent external Data Monitoring Committee monitored unblinded clinical trial data. An independent Cardiovascular Adjudication Committee blindly adjudicated all deaths and potential cardiovascular (CV) events, including potential arterial and venous thromboembolic events (VTEs). Major adverse cardiovascular events (MACEs) included CV death, non-fatal myocardial infarction and non-fatal stroke. VTEs included deep vein thrombosis and pulmonary embolism (PE). Active/latent TB events and potential gastrointestinal (GI) perforations were assessed by the sponsor.

Statistical analyses

Baseline characteristics and exposure (last dose date minus first dose date plus 1, 7 and 14 days for upadacitinib, MTX and adalimumab) were summarised descriptively. TEAEs were summarised using the MedDRA version 19.1 system organ class and preferred term.

Exposure-adjusted event rates (EAERs) per 100 patient-years (PY) were summarised as events based on the treatment received at the time of each AE; multiple events occurring in the same patient were included in the numerator. 95% CIs were calculated using the Cochran-Mantel-Haenszel test (adjusted for each study). Exposure-adjusted incidence rates (EAIRs) per 100 PY were summarised as the number of patients with ≥ 1 event/100 PY (E/100 PY), with exposure calculated up to onset of the first event; 95% CIs were calculated using the exact method for the Poisson mean. Mean changes from baseline in laboratory parameters and vital signs were summarised.

HRs (95% CIs) for upadacitinib versus comparators were calculated using a Cox proportional hazards model including the prognostic factors of the treatment group and baseline covariates. Risk factors for herpes zoster (HZ) in upadacitinib-treated patients were identified using a univariate Cox regression model.

The standardised incidence ratio (SIR) for malignancy excluding non-melanoma skin cancer (NMSC) was calculated using age- and gender-specific malignancy data from the US National Cancer Institute Surveillance and Epidemiology and End Results database, 18 Registry Research Data 2000–2015; 95% CIs were calculated following a Poisson distribution. The standardised mortality ratio (SMR) used the WHO country-specific, age-specific and gender-specific death data for the general population; 95% CIs were calculated using Byar's approximation.

RESULTS

Patients and exposure

Across studies, 3834 patients received one or more doses of upadacitinib (15 mg once daily, n=2630; 30 mg once daily, n=1204)

Table 1 Demographics and baseline disease characteristics

Mean (SD) or n (%), unless specified	PBO pooled, n=1042	MTX pooled, n=530	ADA 40 mg EOW, n=579	UPA all phase III long term	
				Any UPA 15 mg once daily, n=2630	Any UPA 30 mg once daily, n=1204
	Short-term data up to 12/14 weeks	Long-term MTX monotherapy Mean exposure: 36 weeks (data censored at rescue)	Long-term ADA Mean exposure: 42 weeks (includes UPA→ADA post-switch)	Long-term UPA (monotherapy or in combination with MTX/ other csDMARDs) Mean exposures: 53 weeks (UPA 15 mg) and 59 weeks (UPA 30 mg)	
Female	822 (78.9%)	419 (79.1%)	470 (81.2%)	2102 (79.9%)	948 (78.7%)
Age, years	54.8 (12.2)	54.1 (12.2)	54.1 (11.7)	54.1 (12.1)	55.3 (11.9)
Geographic region					
North America	321 (30.8%)	110 (20.8%)	122 (21.1%)	689 (26.2%)	429 (35.6%)
South/Central America	181 (17.4%)	121 (22.8%)	126 (21.8%)	529 (20.1%)	153 (12.7%)
Western Europe	92 (8.8%)	45 (8.5%)	29 (5.0%)	200 (7.6%)	129 (10.7%)
Eastern Europe	360 (34.5%)	164 (30.9%)	249 (43.0%)	934 (35.5%)	351 (29.2%)
Asia	37 (3.6%)	54 (10.2%)	18 (3.1%)	135 (5.1%)	85 (7.1%)
Other	51 (4.9%)	36 (6.8%)	35 (6.0%)	143 (5.4%)	57 (4.7%)
Time since RA diagnosis, years	9.0 (8.5)	3.9 (6.0)	8.2 (8.0)	7.7 (8.1)	7.0 (8.3)
Median (range)	6.4 (0.3 to 49.8)	1.2 (0.03 to 38.0)	5.5 (0.3 to 51.1)	4.8 (0.04 to 54.2)	3.7 (0.03 to 51.3)
DAS28-CRP	5.8 (0.9)	5.8 (1.0)	5.2 (1.3)	5.3 (1.3)	5.4 (1.2)
CRP, mg/L	16.5 (20.2)	18.5 (20.5)	14.2 (20.5)	17.0 (21.5)	15.9 (19.8)
Concomitant csDMARD at baseline					
MTX alone	914 (87.9%)	NA	576 (99.5%)	1769 (67.3%)	380 (31.6%)
MTX plus other csDMARD	68 (6.5%)	NA	0	103 (3.9%)	81 (6.7%)
csDMARD other than MTX	58 (5.6%)	NA	0	105 (4.0%)	100 (8.3%)
Prior bDMARD use	261 (25.0%)	0	57 (9.8%)	406 (15.4%)	281 (23.3%)
Concomitant steroids	573 (55.0%)	279 (52.6%)	349 (60.3%)*	1446 (55.0%)†	570 (47.3%)†
Seropositive (RF or ACPA)	880 (84.5%)	424 (80.0%)	497 (85.8%)	2237 (85.1%)	948 (78.7%)
Prior history of herpes zoster	58 (5.6%)	20 (3.8%)	22 (3.8%)	110 (4.2%)	87 (7.2%)
Prior history of herpes zoster vaccination	52 (5.1%)	17 (3.2%)	15 (2.6%)	80 (3.0%)	72 (6.0%)
Positive TB test at screening	124 (12.0%)	66 (12.5%)	77 (13.3%)	299 (11.4%)	119 (9.9%)
CV risk factors at baseline					
Medical history of hypertension	425 (40.8%)	203 (38.3%)	248 (42.8%)	1043 (39.7%)	481 (40.0%)
Diabetes mellitus	77 (7.4%)	36 (6.8%)	41 (7.1%)	212 (8.1%)	90 (7.5%)
History of tobacco/nicotine use (current+former)	371 (35.6%)	207 (39.1%)	199 (34.4%)	998 (37.9%)	509 (42.3%)
Elevated LDL-C (≥ 3.36 mmol/L)	275 (26.6%)	163 (30.9%)	200 (34.5%)	723 (27.5%)	318 (26.5%)
Lowered HDL-C (≤ 1.55 mmol/L)	594 (57.0%)	301 (56.8%)	283 (48.9%)	1504 (57.2%)	705 (58.6%)
Statin use at baseline	128 (12.3%)	60 (11.3%)	58 (10.0%)	300 (11.4%)	168 (14.0%)

All percentages calculated are on non-missing values.

*Baseline is redefined as start of ADA.

†Baseline is redefined as start of UPA.

ACPA, anti-citrullinated protein antibody; ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; DAS28-CRP, Disease Activity Score for 28 joints-CRP; EOW, every other week; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MTX, methotrexate; NA, not applicable; PBO, placebo; RA, rheumatoid arthritis; RF, rheumatoid factor; TB, tuberculosis; UPA, upadacitinib.

for a mean duration of approximately 1 year and 4020.1 PY of exposure. Sixty-six per cent (15 mg, 61%; 30 mg, 75%) and 4% (15 mg, 4%; 30 mg, 5%) of patients received ≥ 48 and ≥ 96 weeks of upadacitinib treatment, respectively, with a maximum exposure of 2.5 years. Most patients were female and had been diagnosed with RA for a median of 1.2–6.4 years (table 1).

Overview of AEs

The most common TEAEs (≥ 10 E/100 PY) with upadacitinib were upper respiratory tract infection, nasopharyngitis, urinary tract infection and, for upadacitinib 30 mg only, increased blood CPK (online supplemental table S2). The EAER of serious TEAEs (SAEs) with upadacitinib 15 mg was comparable with adalimumab but higher than MTX (table 2).

SAE rates were higher with upadacitinib 30 versus 15 mg. Pneumonia was the most common SAE reported with both upadacitinib doses.

There were 22 treatment-emergent deaths reported with upadacitinib (n=11 each for upadacitinib 15 and 30 mg): 10 adjudicated CV deaths and 12 non-CV deaths (online supplemental material). Compared with the general population, the SMR for treatment-emergent deaths in the upadacitinib groups was 0.58 (95% CI: 0.37 to 0.85). There were two, one and four deaths among the placebo, MTX and adalimumab groups, respectively.

Rates of AEs, AESIs and laboratory abnormalities were generally similar between the upadacitinib monotherapy population (online supplemental table S3) and the overall upadacitinib population.

Table 2 TEAEs in patients with upadacitinib compared with placebo and active controls*

	PBO pooled, n=1042	MTX pooled, n=530	ADA 40 mg EOW, n=579	UPA all phase III long term	
				UPA 15 mg once daily, n=2630	UPA 30 mg once daily, n=1204
E/100 PY (95% CI), unless stated otherwise	Short-term data up to 12/14 weeks	Long-term MTX monotherapy Mean exposure: 36 weeks (data censored at rescue)	Long-term ADA Mean exposure: 42 weeks (includes UPA→ADA post-switch)	Long-term UPA (monotherapy or in combination with MTX/other csDMARDs) Mean exposures: 53 weeks (UPA 15 mg) and 59 weeks (UPA 30 mg)	
Total PY of exposure, years	256.8	368.7	467.8	2655.1	1365.0
Median exposure, days (range)	97.0 (1 to 128)	179.5 (7 to 865)	257.0 (14 to 894)	375.0 (2 to 898)	431.0 (1 to 857)
Any AE	447.4 (421.9 to 474.1)	321.7 (303.6 to 340.5)	294.8 (279.4 to 310.8)	295.7 (289.2 to 302.3)	368.7 (358.6 to 379.0)
Any SAE	9.3 (6.0 to 13.9)	11.9 (8.7 to 16.0)	15.6 (12.2 to 19.6)	15.0 (13.6 to 16.6)	21.3 (18.9 to 23.9)
Any AE leading to discontinuation	10.9 (7.2 to 15.8)	9.5 (6.6 to 13.2)	11.1 (8.3 to 14.6)	8.4 (7.4 to 9.6)	13.3 (11.5 to 15.4)
Deaths†	0.8 (0.1 to 2.8)	0.3 (0.0 to 1.5)	0.9 (0.2 to 2.2)	0.5 (0.3 to 0.8)	1.0 (0.5 to 1.7)

*Patients who switched from PBO, ADA or MTX to UPA were included in the UPA analysis set from the start of UPA treatment, while those who switched from UPA to ADA were included in the ADA dataset from the start of ADA. There was no switch between UPA doses in any study.
 †Deaths included non-treatment-emergent deaths that occurred >30 days after the last dose of study drug (UPA 15 mg, 3; UPA 30 mg, 3; and ADA, 1). When non-treatment deaths are included, the exposures are 2925.0 PY for UPA 15 mg and 1410.3 PY for UPA 30 mg.
 ADA, adalimumab; AE, adverse event; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; MTX, methotrexate; PBO, placebo; E/100 PY, event per 100 patient-years; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

AEs of special interest

EAERs (figure 1) and EAIRs (online supplemental figure S1) of AESIs are summarised by treatment.

Serious infection EAERs were similar between the upadacitinib 15 mg and adalimumab groups, both of which were higher versus MTX; the EAER was higher for upadacitinib 30 mg versus 15 mg (figure 1). Cox regression analyses showed that upadacitinib 30 mg, but not 15 mg, was associated with an increased risk of serious infections versus placebo and adalimumab (online supplemental table S4). The serious infection EAER in the

upadacitinib 15 mg group did not increase over time, although some increases were observed in the upadacitinib 30 mg group between 6 and 12 months on treatment (online supplemental figure S2).

EAERs of opportunistic infections were similar across treatment groups, with the highest rate observed in the upadacitinib 30 mg group (figure 1). The majority of opportunistic infections observed with upadacitinib were mucosal candida infections. There were three events (0.1 E/100 PY) of serious opportunistic infections among patients receiving upadacitinib 15 mg

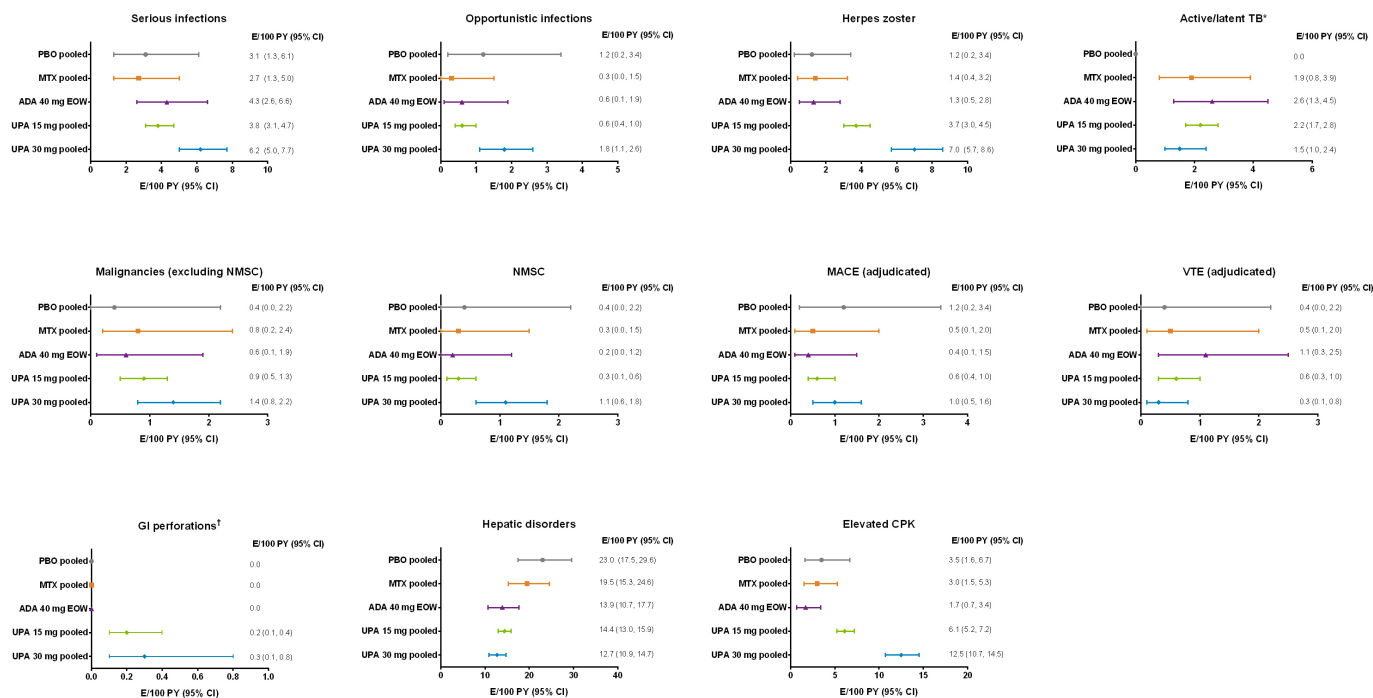


Figure 1 Event rates for AESIs. Additional details on AESIs are included in the online supplemental material. Incidence rates are shown in online supplemental figure S1.

*EAERs for active TB in E/100 PY: PBO, 0; MTX, 0; ADA, 0.2; UPA 15 mg, 0.1; UPA 30 mg, 0.1.
 †Including all potential GI perforations; EAERs for confirmed GI perforations in E/100 PY: PBO, 0; MTX, 0; ADA, 0; UPA 15 mg, <0.1; UPA 30 mg, 0.3.
 ADA, adalimumab; AESI, adverse event of special interest; CPK, creatine phosphokinase; E/100 PY, event per 100 patient-years; EAER, exposure-adjusted event rate; EOW, every other week; GI, gastrointestinal; MACE, major adverse cardiovascular event; MTX, methotrexate; NMSC, non-melanoma skin cancer; PBO, placebo; TB, tuberculosis; UPA, upadacitinib; VTE, venous thromboembolic event.

(bronchopulmonary aspergillosis, HZ disseminated and cryptococcal pneumonia) and none in the upadacitinib 30 mg group.

EAERs of HZ were greater with upadacitinib versus placebo, adalimumab and MTX (figure 1). Upadacitinib was associated with a higher risk of HZ than comparator groups (online supplemental table S4). Most HZ cases in the upadacitinib 15 and 30 mg groups were non-serious (96% and 93%) and involved a single dermatome (74% and 76%). There was one serious event of disseminated HZ, two non-serious ophthalmic HZ events and five non-serious postherpetic neuralgia events with upadacitinib 15 mg; and one non-serious event of disseminated HZ, one serious ophthalmic HZ event and six non-serious postherpetic neuralgia events with upadacitinib 30 mg. Both events of disseminated HZ had cutaneous involvement only. No deaths occurred as a result of HZ. Among patients treated with upadacitinib 15 mg, those who were Asian, aged ≥ 50 years or had a history of HZ had a higher risk of HZ (online supplemental table S5). At baseline, 2.6%–6.0% of patients across treatment groups reported a history of HZ vaccination. However, there was no evidence that prior HZ vaccination decreased HZ risk in upadacitinib-treated patients in this analysis.

EAERs of active/latent TB were similar between the upadacitinib, adalimumab and MTX groups; and no active/latent TB was reported in the placebo group (figure 1). Six patients had non-fatal active TB: three with upadacitinib 15 mg, two with 30 mg and one with adalimumab (online supplemental material). The overall rate of active TB was 0.1 E/100 PY (five events; exposure: 4020.1 PY) with upadacitinib.

The EAERs of NMSC and malignancies excluding NMSC were generally comparable across treatment groups, with the highest rates observed with upadacitinib 30 mg (figure 1). The age- and gender-adjusted SIR (95% CI) for non-NMSC malignancies with upadacitinib 15 mg, 1.05 (0.66 to 1.60), was within the expected range for the general US population. The observed types of non-NMSC malignancies reflected those expected in patients with RA (online supplemental material).

Nine potential GI perforations were identified with upadacitinib, occurring between 73 and 341 days after treatment initiation, and no events with placebo, MTX or adalimumab. Two of the five events (<0.1 E/100 PY) in the upadacitinib 15 mg group and all four events (0.3 E/100 PY) in the 30 mg group were assessed as GI perforations by the sponsor (online supplemental material).

EAERs of adjudicated MACE were comparable across treatment groups and did not increase over time with upadacitinib treatment (figure 1; online supplemental table S6; online supplemental figure S3). Dose-dependent increases in total cholesterol and low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were observed with upadacitinib treatment. LDL-C/HDL-C ratios remained constant throughout, with no apparent association of LDL-C levels with occurrence of MACE.

EAERs of adjudicated VTE were comparable across treatment groups (figure 1; online supplemental table S6). There was one fatal PE in the upadacitinib 15 mg group in a woman aged 55 years who developed PE after prolonged driving. There was no evidence of a dose relationship in VTE rate with upadacitinib nor a pattern of time-to-VTE-onset (23–1127 days of upadacitinib treatment). VTE in upadacitinib groups did not appear to be associated with increased platelet count (online supplemental material). There were two events of arterial thrombosis in the upadacitinib 30 mg group and none in the 15 mg group (online supplemental material).

Laboratory abnormalities

Slight decreases in haemoglobin were observed with upadacitinib 30 mg but not 15 mg (mean change from baseline at week 12 of -3.9 and -0.5 g/L, respectively, vs -1.5 g/L with placebo; online supplemental figure S4). The proportion of patients with grade 3/4 decreases in haemoglobin were generally similar between MTX and upadacitinib 15 mg and were highest with upadacitinib 30 mg (table 3).

The proportions of patients with grade 3 decreases in neutrophils were similar across treatment groups, with a greater proportion with upadacitinib 30 mg. Grade 4 decreases in neutrophils were rare. Mean lymphocyte counts increased over the first 36 weeks of treatment, followed by slight decreases afterwards. The proportions of patients with grade 3 decreases in lymphocytes were comparable between MTX and both upadacitinib groups and were higher than those for placebo and adalimumab. Grade 4 decreases were most frequent in the upadacitinib 30 mg group. There was no clear association between infectious events, including HZ, and decreased neutrophil or lymphocyte counts.

The proportions of patients experiencing grade 3 elevations in transaminases were similar between MTX and both upadacitinib groups and were greater than those in the placebo and adalimumab groups. Grade 4 increases occurred in few patients across treatment groups. Most transaminase elevations did not result in treatment discontinuation and resolved or were resolving regardless of whether upadacitinib was discontinued. There were no cases of probable drug-induced liver injury attributable to upadacitinib.

CPK elevations, including grade 3/4 increases, were more frequent with upadacitinib versus placebo, MTX or adalimumab (figure 1; table 3; online supplemental table S4). The greatest rise in CPK levels occurred for both upadacitinib doses at week 4 (50.1 and 74.3 U/L with 15 and 30 mg), after which CPK levels rose less markedly before plateauing around weeks 36 to 48. CPK elevations were typically asymptomatic; few led to discontinuation (two with upadacitinib 15 mg; three with 30 mg). One patient who received upadacitinib 30 mg had a serious event of rhabdomyolysis, with an alternative aetiology of influenza, which resulted in treatment interruption.

DISCUSSION

Based on an integrated analysis of the SELECT clinical trial programme, the overall safety profile of upadacitinib appeared comparable with other JAKis,^{11–13} with no new or unexpected safety risks identified.

Treatment with upadacitinib was associated with an increased risk of HZ and CPK elevations versus placebo, MTX and adalimumab according to Cox regression analyses. Rates of deaths and malignancies with upadacitinib appeared consistent with expected rates from the general population. The serious infection rate observed with upadacitinib 15 mg was similar to that reported for other marketed RA therapies.^{14–16} The rates of serious infections, HZ, CPK elevations and neutropenia were higher for the unapproved upadacitinib 30 mg dose compared with the approved upadacitinib 15 mg dose.

Consistent with previously reported data for other JAKis,^{11 12 17 18} HZ rates were higher with upadacitinib versus placebo, MTX and adalimumab, and higher HZ rates among upadacitinib were observed in older patients and those in Asia. The majority of HZ cases reported with upadacitinib were non-serious and involved a single dermatome. Few patients enrolled in the SELECT programme received HZ vaccination (limited to Zostavax) prior to randomisation. Information about the impact

Table 3 Proportion of patients with potentially clinically significant haematological and clinical chemistry values

n/N Obs (%)	PBO pooled, n=1042	MTX pooled, n=530	ADA 40 mg EOW, n=579	UPA all phase III long term	
				Any UPA 15 mg once daily, n=2630	Any UPA 30 mg once daily, n=1204
	Short-term data up to 12/14 weeks	Long-term MTX monotherapy Mean exposure: 36 weeks (data censored at rescue)	Long-term ADA Mean exposure: 42 weeks (includes UPA→ADA post-switch)	Long-term UPA (monotherapy or in combination with MTX/ other csDMARDs) Mean exposures: 53 weeks (UPA 15 mg) and 59 weeks (UPA 30 mg)	
Haemoglobin (g/L)					
Grade 3 (70 to <80 or decreased 21 to <30)	23/1036 (2.2)	28/526 (5.3)	18/576 (3.1)	150/2622 (5.7)	133/1193 (11.1)
Grade 4 (<70 or decreased ≥30)	8/1036 (0.8)	12/526 (2.3)	6/576 (1.0)	39/2622 (1.5)	49/1193 (4.1)
Platelets (×10⁹/L)					
Grade 3 (20 to <50)	0/1032	0/525	0/576	1/2619 (<0.1)	1/1192 (<0.1)
Grade 4 (<20)	0/1032	0/525	0/576	1/2619 (<0.1)	1/1192 (<0.1)
Neutrophils (×10⁹/L)					
Grade 3 (0.5 to <1.0)	1/1036 (<0.1)	2/526 (0.4)	2/576 (0.3)	22/2622 (0.8)	28/1192 (2.3)
Grade 4 (<0.5)	0/1036	0/526	1/576 (0.2)	7/2622 (0.3)	2/1192 (0.2)
Lymphocytes (×10⁹/L)					
Grade 3 (0.5 to <1.0)	119/1036 (11.5)	79/526 (15.0)	44/576 (7.6)	451/2622 (17.2)	250/1192 (21.0)
Grade 4 (<0.5)	7/1036 (0.7)	5/526 (1.0)	2/576 (0.3)	30/2622 (1.1)	29/1192 (2.4)
Leucocytes (×10⁹/L)					
Grade 3 (1.0 to <2.0)	0/1036	0/526	1/576 (0.2)	9/2622 (0.3)	7/1193 (0.6)
Grade 4 (<1.0)	0/1036	0/526	0/576	0/2622	2/1193 (0.2)
ALT (U/L)					
Grade 3 (3.0 to <8.0× ULN)	13/1037 (1.3)	23/527 (4.4)	9/577 (1.6)	76/2620 (2.9)	37/1195 (3.1)
Grade 4 (>8.0× ULN)	2/1037 (0.2)	5/527 (0.9)	3/577 (0.5)	11/2620 (0.4)	6/1195 (0.5)
AST (U/L)					
Grade 3 (3.0 to <8.0× ULN)	6/1036 (0.6)	13/527 (2.5)	6/577 (1.0)	46/2620 (1.8)	17/1195 (1.4)
Grade 4 (>8.0× ULN)	1/1036 (<0.1)	1/527 (0.2)	4/577 (0.7)	7/2620 (0.3)	5/1195 (0.4)
CPK (U/L)					
Grade 3 (>5.0 to 10.0× ULN)	3/1037 (0.3)	2/527 (0.4)	1/577 (0.2)	38/2620 (1.5)	22/1196 (1.8)
Grade 4 (>10.0× ULN)	0/1037	0/527	1/577 (0.2)	10/2620 (0.4)	11/1196 (0.9)

N Obs indicates the number of patients with baseline and post-baseline values for the respective parameters.

ADA, adalimumab; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; MTX, methotrexate; PBO, placebo; ULN, upper limit of normal; UPA, upadacitinib.

of newer inactivated HZ vaccines (although not yet available worldwide) on the risk of HZ among patients receiving upadacitinib and other JAKis is necessary to inform clinical practice.

VTE is an emerging AESI among patients receiving JAKis,^{23 19–22} but longer-term data are needed to characterise the risk of VTE with JAKi therapy. Patients with RA are at increased risk of VTE (incidence rates 0.3–0.8/100 PY)^{23 24} compared with the general population, with a 2.4-fold increased rate.²⁵ In this analysis, the rates of adjudicated VTE were similar across both doses of upadacitinib, placebo, adalimumab and MTX, with no evidence of a dose relationship with upadacitinib treatment. In view of the increased risk of VTE and underlying VTE risk factors among patients with RA, patients should be promptly evaluated for signs and symptoms of possible thrombosis and appropriately treated during JAKi therapy.

Patients with RA receiving anti-interleukin 6 (IL-6) receptor therapy are at increased risk of GI perforation, with one study reporting a lower GI perforation rate of 0.27 E/100 PY with the IL-6 receptor inhibitor tocilizumab.^{26 27} Although JAKis also inhibit IL-6 signalling,^{28 29} GI perforations with upadacitinib 15 mg (0.08 E/100 PY) were observed at similar rates to tumour necrosis factor inhibitors (0.05 E/100 PY) and other JAKis (0.04–0.10 E/100 PY).^{13 27 29} Upadacitinib 30 mg had higher rates of

GI perforations (0.29 E/100 PY), although this was based on a limited number of events.

Decreases in haemoglobin and neutrophils, and increases in transaminase and CPK, observed with upadacitinib, were consistent with laboratory changes observed with other JAKis.^{12 13} In vitro data suggest that JAKi-associated increase in CPK may represent restoration of myoblast differentiation.³⁰ Most laboratory abnormalities were resolved, and most patients experiencing them were able to remain on the study drug. Although engineered for increased JAK1 selectivity,¹ the effects of upadacitinib on parameters such as haemoglobin suggest that upadacitinib (particularly the unapproved 30 mg dose) may have some effects on JAK2. However, maximal efficacy of upadacitinib was achieved at the 15 mg dose with comparable safety to the approved doses of other JAKis, with no additional efficacy benefit observed with the 30 mg dose.^{23 31} In contrast, the use of less selective JAKis at higher doses is associated with improved efficacy but is limited due to increased safety risks.^{21 32–35}

The limited placebo exposure time prevented the placebo-controlled analysis of longer-term safety. However, longer-term controlled data versus MTX monotherapy (SELECT-EARLY) and adalimumab (SELECT-COMPARE) offer the opportunity to compare the safety profile of upadacitinib to other RA therapies.

As patients were not allowed to change upadacitinib doses, this allowed an unadulterated comparison of the safety profile of the upadacitinib 15 and 30 mg doses. While upadacitinib monotherapy was well tolerated with comparable safety to the overall upadacitinib population, further analyses are required to identify any differences in long-term safety between upadacitinib administered as monotherapy and in combination with csDMARDs. Despite a robust trial programme, the data remain limited by exposures to date, with ongoing monitoring still underway. As these data are from RCTs with specific eligibility criteria and clear follow-up protocols, this may limit the generalisability of these results to clinical practice. Monitoring by a specialist is recommended for oral treatments such as upadacitinib, as with all antirheumatic therapies.

Based on integrated data from five phase III RCTs, with 3834 patients and 4020.1 PY of exposure, no new safety risks emerged with upadacitinib compared with other approved JAKis. These results support an acceptable safety profile of upadacitinib 15 mg once daily for the treatment of moderately to severely active RA. Follow-up of patients receiving upadacitinib will continue in long-term extensions of clinical trials and postmarketing studies.

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